REMARKS

As instructed by the Examiner, Applicants have amended the first line of the specification of this application to provide a proper cross-reference to related applications. In particular, the amendment states that this application is the U.S. national stage of corresponding PCT application PCT/US98/22145, filed October 20, 1998, and claims the benefit of United States Provisional Application No. 60/109,804, filed October 20, 1997 (now expired).

Applicants acknowledge that the Examiner has made final a restriction requirement for the claims (see, Office Action dated June 20, 2001) over Applicants' traverse. Accordingly, the Examiner has withdrawn Claims 38, 39, 49, and 50. Claims 40-48 and 51-52 are pending for examination in this application.

Response to Rejections Under 35 U.S.C. § 112, first paragraph

In the Office Action, the Examiner rejected Claims 40-48, 51, and 52 under 35 U.S.C. §112, first paragraph, objecting to the scope of the claims and written description in support of the claims.

The Examiner rejected Claims 40-48 and 51-52 as overly broad and requiring undue experimentation based on the argument set forth on pp. 3-9 of the office action. In particular, the Examiner considered that the specification did not enable the claimed methods comprising administering to "any" mammal "any" non-endogenous cholesteryl ester transfer protein (CETP) in an amount effective to reduce CETP activity in the blood to a level that is less than 20% of that in the untreated mammal (Claim 40), to achieve an unexpectedly low level of circulating CETP, i.e., essentially 0 μg CETP per milliliter of blood (Claim 41), or to achieve an anti-atherogenic lipoprotein profile in the blood of the mammal wherein there is an unexpectedly high level HDL-cholesterol (Claims 42, 43) or unexpectedly low level of LDL-cholesterol (Claims 44, 45). The Examiner further rejected as inadequately enabled Applicants' claimed methods as applied to humans (Claims 46, 48) or as employing a preferred group of whole, non-endogenous CETP molecules (Claim 47). Finally, the Examiner rejected as not enabled Applicants' claimed methods wherein adjuvants are employed (Claims 51, 52). The Examiner relied on the following documents to support the rejections:

Ngo et al., "Computational Complexity, Protein Structure Prediction, and the Levinthal Paradox," *In* The Protein Folding Problem and Tertiary Structure Prediction (Merz and Le Grand, eds.) (Birkhauser, Boston, 1994), pp. 492-495 from Chapter 14 (hereinafter "Ngo");

Kuby, *In* Immunology, Second Edition (W.H. Freeman and Co., New York, 1994), pp. 85-96 from Chapter 4 (hereinafter "Kuby");

Marotti et al., "Severe atherosclerosis in transgenic mice expressing simian cholesteryl ester transfer protein," *Nature, 364*: 73-75 (1993) (of record, hereinafter "Marotti");

Breslow, "Transgenic mouse models of lipoprotein metabolism and atherosclerosis," *Proc. Natl. Acad. Sci. USA, 90*: 8314-8318 (1993) (of record, hereinafter "Breslow");

Stevens, "Use of Synthetic Peptides for Developing a Vaccine Against Human Chorionic Gonadotropin," *In* Synthetic Vaccines, Volume II (CRC Press, Inc., Boca Raton, 1987), pp. 11-133 in Chapter 18 (hereinafter "Stevens").

For the reasons given below, Applicants submit that the claims are adequately enabled and supported by an adequate written description. Accordingly, Applicants respectfully traverse the rejections.

Applicants' claims are directed to methods of using a whole, non-endogenous CETP to produce a particular, measurable, anti-atherogenic condition of unexpected proportions. In particular, Applicants have discovered that administering a whole, non-endogenous CETP to a mammal will elicit production of antibodies that react with the mammal's own, endogenous CETP resulting in:

- an unexpectedly low level of circulating CETP molecules (essentially no detectable CETP per ml of blood plasma) or of CETP activity (below 20% of the activity in an untreated mammal),
- an unexpectedly high level of blood cholesterol in the form of "good cholesterol", i.e., HDL-cholesterol (greater than 90%, and as high as 100%),
- an unexpectedly low level of blood cholesterol in the form of "bad cholesterol", i.e., LDL-cholesterol (less than 10%, and as low as, essentially, none).

Examples of achieving such measurable results according to Applicants' claimed methods are provided in the specification, using a well known rabbit model for atherosclerosis (see, Example 1 at p. 16, line 26, to p. 20, line 21, of the specification). When rabbits were switched to a high

cholesterol (atherogenic) diet, rabbits vaccinated with a whole, non-endogenous CETP had a demonstrably lower incidence of atherosclerotic lesions (see, Figure 14).

The Examiner considered the claims as overly broad and requiring undue experimentation supposedly because a person skilled in the art allegedly would be unable to predict whether any whole, non-endogenous CETP would work in the claimed invention. However, nowhere has the Examiner provided any evidence that would reasonably contravene what Applicants have demonstrated, using an animal model for atherosclerosis that is well known and widely used by persons skilled in this art. The Examiner has not provided any facts to indicate why a person skilled in this art who reads Applicants' specification and follows the directions and teachings for carrying out the essential steps of the claimed methods should not reasonably expect the *in vivo* results taught and demonstrated (e.g., in Example 1) in Applicants' specification. In contrast to the Examiner's speculation, Applicants have provided an *in vivo* working example that used the rabbit model for atherosclerosis, which is known and relied on by persons skilled in this art for studying and developing methods of treating atherosclerosis. Obviously, such models are used in this art to obtain a reasonable basis for understanding compositions and methods for treating mammalian, and especially human, coronary artery disease without the enormous expense and time limitations that would be necessary to study *every* mammal. Optimization for a particular mammalian species is not undue experimentation, and it is not required by the statute that an inventor in this art to provide a species by species optimization for results to be reasonably understood and believed by persons skilled in this art, especially when the practice and expectation of those skilled in this art is to use an accepted animal model for atherosclerosis.

Despite Applicants' demonstration of success in practicing the claimed invention in a format understood by those skilled in this art, the Examiner appears to have focused on whether a person skilled in the art could select the correct non-endogenous CETP for *any* mammal treated according to the claimed methods. Applicants note that, except in the case of novel molecules, the inventive feature of the claimed **methods** does not reside in a particular non-endogenous CETP employed. Persons skilled in this art are assumed to already know or to know how to easily determine whether one CETP is the same or different, i.e., non-endogenous, from the endogenous CETP in a particular mammalian subject. Much is already known by persons skilled in this art regarding CETP molecules of various mammalian species (see, e.g., Tall, *J. Lipid Res.*,

34: 1255-1274 (1993) (review on CETP, of record)) and whether various mammalian species even express an authentic CETP molecule in the blood (see, e.g., Breslow, *supra*, at p. 8317; Ha et al., *Comp. Biochem. Physiol., 71B*: 265-269 (1982) (early survey of CETP activities in various mammalian species, of record).

Determination of whether a CETP molecule is non-endogenous to the subject to be treated according to the invention is within the skill in the art. Even if the source of a CETP molecule is unknown, determination of whether a mystery CETP is non-endogenous to a mammal to be treated is easily determined by those skilled in this art using no more than routine analytical procedures. Such routine analytical procedures include, but are not limited to, molecular weight determinations on denaturing gels, various immunoblotting techniques to detect amounts and relatedness of various CETP molecular species (e.g., Western immunoblots, ELISA assays), amino acid sequence analysis, nucleotide sequence analysis, and CETP activity assays (see, e.g., Examples 1-3 in the present specification; Bisgaier et al., *J. Lipid Res., 34*: 1625-1634 (1993) (CETP assay); Drayna et al., *Nature, 327*: 632-634 (1987) (cloning and sequence analysis); Nagashima et al., *J. Lipid Res., 29*: 1643-1649 (1988) (cloning and sequence analysis); Ha et al., *Comp. Biochem. Physiol., 71B*: 265-269 (1982) (survey of CETP activity exhibited in various mammalian species), all of record). Such methods may be applied to all naturally occurring CETPs, including xenogenic and allelic variants, which may be expressed in an individual mammalian species.

In addition, without cataloguing every possibility, Applicants submit that persons skilled in this art reasonably expect the existence of both xenogenic and allelic variants of a mammalian protein, including the circulating protein, CETP. Furthermore, persons skilled in this art recognize that a non-endogenous CETP may be a non-naturally occurring molecule derived from a naturally occurring CETP, e.g., by modifying one or more amino acid residues using *in vitro* methods to more closely resemble, but not be identical to, the CETP of the mammal being treated, i.e., a "mammalianized", non-endogenous CETP molecule as discussed in the specification (see, e.g., p. 8, line 22, to p. 9, line 17, of the specification) and illustrated by "humanized rabbit" CETPs of SEQ ID NOs:5 and 6. Accordingly, persons skilled in this art are able to select and determine a CETP that is non-endogenous to the CETP of a particular subject to be treated, without undue experimentation.

Applicants further note that persons skilled in the art who follow Applicants' teachings are able to quickly determine whether a particular desired anti-atherogenic effect as recited in Applicants' claims is achieved, i.e., by using such standard assays to determine the blood plasma levels of CETP (level of protein *per se*), CETP activity (level of transfer activity), cholesterol level, LDL-cholesterol level, and/or HDL-cholesterol level. Thus, neither the selection of a non-endogenous CETP nor the determination of whether the recited endpoints have been reached in practicing Applicants' claims require undue experimentation on the part of persons skilled in this art. The Examiner has not explained why skilled persons in this art cannot follow the direct examples of the specification, even substituting other mammalian subjects for rabbits and other CETP molecules non-endogenous to the subject, then determining in the same way as demonstrated whether a particular endpoint recited in a claim is reached. It is respectfully submitted that the ability to follow Applicants' demonstrations is within the skill of persons skilled in this art.

Applicants note that for enablement under 35 U.S.C. §112, first paragraph, it is sufficient that a person skilled in the art is either shown by example or directed to obtain elements in a claim, even if the person may have to carry out some confirmatory experimentation using routine methodology. *See*, e.g., *Atlas Powder Co. v. E.I. Du Pont DeMours & Co.*, 750 F.2d 1569, 1576, 224 USPQ 409, 413 (Fed. Cir. 1984) (*citing W.L. Gore & Associates v. Garlock, Inc.*, 721 F.2d 1540, 1557, 220 USPQ 303, 316 (Fed. Cir. 1983), and *In re Angstadt*, 537 F.2d 498, 504, 190 USPQ 214, 219 (CCPA 1976)).

By the Examiner's standard (which is not the standard set by 35 U.S.C. §112), patent coverage is only available for an applicant's specific examples (such as Example 1 in the present specification). More specifically, it appears that the Examiner fails to appreciate the knowledge and skill of persons skilled in this particular art and how the skilled practitioner in this field relies on data from well known mammalian models (e.g., rabbits, transgenic mice, transgenic rats) employed in biochemical and pharmacological studies of lipoprotein/cholesterol metabolism and treatments for atherosclerosis (see, e.g., Tall, *J. Lipid Res.*, *34*: 1255-1274 (1993), of record; Shih et al., *Molec. Med. Today* (Elsevier Sceince, Ltd., 1995), pp. 364-372, **copy attached**). By the Examiner's standard of patentability, no applicant could ever obtain useful patent coverage in this field unless a working example of each and every possible embodiment of the invention (i.e., trying every possible whole, non-endogenous CETP in every mammalian species) was actually

printed in the application. This would be an impossible requirement to meet and is clearly not a requirement of United States patent law or practice. In fact, such an onerous and unreasonable standard has been expressly repudiated by the courts:

> "**What the Patent Office is here apparently attempting is to limit all claims to the specific examples, notwithstanding the clear disclosure of a broader invention. This it may not do.** As was stated in *American Anode, Inc. v. Lee-Tex Rubber Products Corp.*, 136 F.2d 581, 585 (7th Cir. 1943):
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> 'There is no doubt that a patentee's invention may be broader than the particular embodiment shown in his specification. A patentee is not only entitled to narrow claims particularly directed to the preferred embodiment, but also to broad claims which define the invention without reference to specific instrumentalities. *Smith v. Snow*, 294 U.S. 1 [at pages 11 et seq.] 55 S.Ct. 279, 79 L. Ed. 721.'"

In re Anderson, 471 F.2d 1237, 1241, 176 USPQ 331, 333 (CCPA 1973) (emphasis added). See, also, *In re Goffe*, 542 F.2d 564, 567, 191 USPQ 429, 431 (CCPA 1976) ("'To demand that the first to disclose shall limit his claims to what he has found will work or to materials which meet the guidelines specified for 'preferred' materials in a process such as the one herein involved would not serve the constitutional purpose of promoting progress' (citation omitted)"). Thus, Applicants submit that the teachings, guidance, and examples of the specification clearly and adequately enable and describe persons skilled in this art to carry out the claimed methods.

Applicants briefly comment on the publications cited by the Examiner.

The Examiner referred to Ngo as teaching "that the amino acid positions within the polypeptide/protein that can tolerate change such as conservative substitution or no substitution, addition or deletion which are critical to maintain the protein's structure/function will require guidance" (Office Action, p. 5). Ngo is a commentary on the complexity of finding a computational algorithm to predict protein structure from the protein's amino acid sequence. However, Applicants' claimed methods comprise administering to a mammal a non-endogenous CETP to establish an anti-atherogenic condition. Persons skilled in this art are familiar with CETPs from various species and have known for a decade or longer that mammalian CETPs participate in the lipoprotein-cholesterol metabolism of a variety of mammalian species (see, e.g., Tall, *J. Lipid Res.*, 34: 1255-1274 (1993); Ha et al., *Comp. Biochem. Physiol., 71B*: 265-269 (1982)). In addition, persons skilled in this art know that some mammalian species (such as

species of mice and rats) lack a circulating CETP (see, e.g., Agellon et al., *J. Biol. Chem., 266*: 10796-10801 (1991), **copy attached**; Breslow, *Proc. Natl. Acad. Sci. USA, 90*: 8314-8318 (1993), of record; Marotti, of record (ref. BJ)). Accordingly, Ngo does not provide any evidence to indicate that persons skilled in this art are not already familiar with a variety of CETP molecules and know how to determine whether a CETP molecule differs or is identical to a particular endogenous CETP circulating in a mammalian subject. What is unexpected from the prior art is that Applicants' have discovered that immunizing a mammal with a whole, non-endogenous CETP can eliminate essentially all of the detectable endogenous CETP molecules or activity, convert essentially all of the circulating cholesterol to the form of HDL-cholesterol (good cholesterol), or eliminate essentially all of the detectable LDL-cholesterol (a bad cholesterol) from the circulation.

The Examiner viewed Kuby as indicating that B-cell epitopes are not linear and that it is not possible to predict whether a particular, whole, non-endogenous CETP may elicit endogenous antibodies to a particular subject's endogenous CETP. First, Applicants note that Kuby says more than what the Examiner stated. In fact, Kuby makes clear that a person skilled in this art knows the following: (1) that B-cell epitopes may be composed of a sequence of contiguous residues (linear) along a polypeptide chain or nonsequential (nonlinear) residues from segments of the chain brought together in a folded conformation of the polypeptide and (2) that sequential (linear) epitopes are typically 5 to 8 amino acids in length (see, e.g., Kuby, sentence bridging pp. 94-95; see, also, Watson et al., *In* Molecular Biology of the Gene, Fourth Edition (The Benjamin/Cummings Publishing Co., Inc., 1987), p. 836, **copy attached**; Davis et al., *In* Microbiology, Second Edition (Harper & Row, Hagerstown, 1973), **copy attached**). Furthermore, contrary to the Examiner's view, persons skilled in this art are well aware that mammalian CETP molecules clearly contain some very important linear B-cell epitopes that are composed of a sequence of contiguous amino acids (see, e.g., Wang et al., *J. Biol. Chem., 267*: 17487-17490 (1992); Wang et al., *J. Biol.Chem., 268*: 1955-1959 (1993); Swenson et al., *J. Biol. Chem., 264*: 14318-14328 (1989); of record; see, also, Saito et al., *J. Lipid Res., 40*: 2013-2021 (1999) (**copy attached**).

Applicants further note that whether a B-cell epitope of CETP is linear or nonlinear is irrelevant to their invention. Applicants' specification teaches that administering a non-endogenous CETP to a mammalian subject according to the invention achieves a number of

unexpected, measurable endpoints that have not been previously discovered or taught in **any** prior description of CETP vaccines or studies on CETP in mammals. Kuby provides no evidence that persons skilled in this art, who read Applicants' specification, will not be able to practice Applicants' invention and reasonably expect the results as described and demonstrated in Applicants' specification. Applicants have provided evidence in a recognized animal model for atherosclerosis that the methods of Applicants' invention work, and any person skilled in this art who reads the specification will be able to follow that teaching and determine by routine methods whether a particular endpoint recited in the claims is achieved.

The present invention involves administration of a non-endogenous CETP to a subject until a particular measurable event is achieved; thus, simply administering a non-endogenous CETP to a subject alone does not embody the invention as claimed. Furthermore, if a mammalian subject does not possess an endogenous, circulating CETP, clearly any CETP must by definition be non-endogenous (although such a subject is, obviously, not a competent subject for treatment according to Applicants' methods, since there is no endogenous CETP activity to modulate). Applicants are not required to provide more than the essential steps for carrying out the methods of the claims, and it is not a function of the claims to specifically anticipate and list inoperative embodiments. *See*, e.g., *Atlas Powder Co. v. E.I. Du Pont DeMours & Co.*, 750 F.2d 1569, 1576, 224 USPQ 409, 413 (Fed. Cir. 1984) (*citing In re Dinh-Nguyen* 495 F.2d 856, 858-859, 181 USPQ 46, 48 (CCPA 1974)).

The Examiner incorrectly interprets Marrotti and Breslow, which describe studies on cholesterol metabolism and atherosclerosis in transgenic mice expressing a transgenic human CETP. The Examiner asserts these references show that:

> "not all xenogeneic [non]-endogenous CETP are appropriate for a method of modulating CETP activity, particularly in humans, where atherosclerosis is multi-factorial complex disease."

(see, p. 6 of the Office Action). Applicants do not understand the Examiner's comments, as both Marrotti and Breslow indicate that persons skilled in this art recognize that a high, endogenous, circulating level of CETP **is** correlated with development of atherosclerosis. Thus, a mammalian subject's endogenous CETP is a superb target for Applicants' methods. CETP mediates transfer of cholesterol from HDL-cholesterol (widely known as "good cholesterol") to VLDL-cholesterol and LDL-cholesterol (widely known as "bad cholesterol"). As noted above, various strains of

mice are well known to **lack** a circulating endogenous CETP (see, e.g., second sentence of the section entitled "CETP Transgenic Mice" in the middle column of p. 8316 of Breslow). As Breslow notes, such mice (which lack their own circulating endogenous CETP) are resistant to atherosclerosis, which is completely consistent with the absence of a circulating, endogenous CETP. Thus, as in Marrotti, it is possible to produce transgenic mice, which by genetic engineering express an endogenous transgenic CETP that acts as an endogenous self-protein, provides researchers with another animal model **because, as in the rabbit model, the development of a severe atherosclerosis can be switched on in such transgenic mice by providing a high cholesterol diet**. Clearly, persons skilled in this art who read Marrotti and Breslow would understand that a mammal's own, endogenous CETP is a valid target for modulation, and Applicants' methods provide a novel means of modulating endogenous CETP activity. Accordingly, Marotti and Breslow demonstrate that persons skilled in this art understand that a constitutive, high circulating level of an endogenous CETP (whether the product of a natural gene or a transgene) is correlated with an atherogenic lipoprotein profile and the development of atherosclerosis.

Finally, the Examiner considered Claims 46 and 48 as not enabled for lack of specific examples of practicing the invention for humans. The Examiner further stated:

> "Furthermore, since CETP is a 'self' protein, it is not clear in the specification as filed how administering a whole recombinant human CETP (which is not foreign and no different than one's own CETP) would induce endogenous **antibody** direct[ed] toward one's own CETP at a level **sufficient[ly] high** to modulate one's own level of endogenous CETP activity. Stevens *et al* teach in order [to] induce high levels of antibodies reactive to one's own protein (break immune tolerance) such as hCG for a contraceptive vaccine, the protein must be conjugated to a foreign protein or carrier molecule such as KLH or tetanus toxoid to enhance the immunogenicity of the hCG protein."

(see, p. 7 of the Office Action, bold in original, underlining added).

Applicants first note that the claimed methods of the application require the administration of a non-endogenous, whole CETP to a mammalian subject. The term "non-endogenous" means that the CETP used in the method is different from and is not the "self" (endogenous) CETP of the subject.

Stevens reviews vaccine compositions for eliciting production of endogenous antibodies to the peptide hormone human chorionic gonadotropin (hCG). The vaccine compositions are made up of hCG polypeptide linked to a carrier molecule. The composition is designed to raise an antibody response against endogenous hCG to inhibit the hormone's activity *in vivo*, with the result of controlling fertility.

The hCG polypeptide is a reproductive hormone, 236 amino acids in length (i.e., approximately one-half of the size of mammalian CETPs), which is produced in a transient pulsatile manner, often at less than microgram per liter amounts, which promotes implantation of a fetus in the womb. In contrast, mammalian CETPs are constitutively produced plasma proteins that are nearly 500 amino acids in length, are involved in the complex cascade of cholesterol metabolism and other processes, and are present in the blood at the level of milligrams per liter (that is 1000-fold higher levels than hCG, when it is in circulation).

Clearly, whatever Stevens may teach about producing vaccines for modulating a hormone of the endocrine system does not provide guidance to persons skilled in the art for modulating the level or activity of an endogenous, constitutively produced, circulating CETP to achieve the specified anti-atherogenic conditions recited in the claims.

With respect to providing support for treating humans, Applicants refer to the above comments regarding the prevalent use of animal studies and established animal models in this field. Obviously, studies in this field are typically carried out in well known animal models with the goal for understanding and treating atherosclerosis in humans. As noted above, Applicants are not limited to their specific examples. *See*, *In re Anderson*, 471 F.2d 1237, 1241, 176 USPQ 331, 333 (CCPA 1973). As also explained above, identification and selection of a CETP, which is non-endogenous with respect to a particular mammalian subject, such as a human subject, is either known or easily determined without undue experimentation. Applicants have thus provided **strong** evidence in support of their claimed methods for producing unexpected anti-atherogenic conditions in humans and other mammals using a mammalian model for persons skilled in this art to understand, practice, and reasonably expect to obtain the results of Applicants' claimed invention as applied to humans and other mammals.

Accordingly, Applicants submit that the above comments make clear that in the absence of any substantial evidence that Applicants' methods would not work, persons skilled in this art who read Applicants' specification, including the successful examples, would know how to select

a non-endogenous CETP for use in the claimed methods and would reasonably expect such methods to achieve a particular, measurable, result in any mammal, including humans.

In view of the above comments, Applicants respectfully request that the Examiner reconsider and withdraw the rejections to the claims based on lack of enabling disclosure.

The Examiner also rejected Claims 40-48, 51, and 52 as containing subject matter not described in the specification. Citing *University of California v. Eli Lilly Co.*, 119 F.3d 1559, 43 USPQ2d 1398, the Examiner was of the view that the specification did not adequately describe the use of any whole, non-endogenous CETP in any mammal to achieve the dramatic anti-atherogenic endpoints in the claimed methods. Applicants respectfully traverse the rejection.

The requirement of a written description of the invention does not mean that Applicants' specification must describe **all** possible species of CETP in **all** possible species of mammals to adequately describe the claimed methods of achieving a specific anti-atherogenic condition. Applicants' written specification clearly indicates that at the time of filing Applicants were in possession of their methods for administering a non-endogenous CETP to a subject and determining whether measurable endpoints are reached. In *Eli Lilly Co.*, 119 F.3d 1559, 43 USPQ2d 1398, cited by the Examiner, the court needed to determine whether a claimed composition to a DNA molecule containing a nucleotide sequence encoding human insulin was adequately described to demonstrate possession by the inventors. The specification in *Lilly* described methods that could be used to discover insulin encoding DNA sequences, but did not make any such sequences apparent to those who read the specification. *Lilly*, 119 F.3d at 1567, 43 USPQ2d at 1405. Since the specification provided no description of the claimed novel sequence, the claimed composition was invalid. *Lilly*, 119 F.3d at 1569, 43 USPQ2d at 1407. Thus, *Lilly* articulates the rule that one cannot obtain a claim to a composition when the very inventive feature of the claimed composition (in that case, its DNA sequence) is not disclosed but merely speculated to exist.

In contrast to *Lilly*, Applicants have already noted that the inventive feature of their claimed **methods** does not reside in whether or not a particular CETP molecule employed in the methods is patentable. Novel CETP molecules are not the subject of the claims under examination in this application. On the contrary, the inventive feature of Applicants' methods resides in the discovery that administering to a mammalian subject a whole, non-endogenous CETP will produce an anti-atherogenic condition of dramatic and heretofore unexpected

proportions, affecting the levels of CETP mass, CETP activity, or lipoprotein species circulating in the treated subject. Applicants' description provides an actual demonstration of the claimed invention using an established animal model in this field. Furthermore, as noted above, persons skilled in this art who read the specification are fully knowledgeable about what is meant by a CETP being "non-endogenous" to that of a particular mammalian subject. *See*, e.g., p. 8, line 13, to p. 9, line 17, of the specification and the discussion above. In additon, the specification provides examples of achieving precise endpoints for the anti-atherogenic conditions of each claimed method (see, Example 1, Figures 8 and 9) and shows that only routine methods are necessary for administering a non-endogenous CETP to a mammalian subject (see, e.g., p. 15, line 5, to p. 16, line 22; Example 1, Figures 8 and 9 of the specification). Thus, Applicants' specification provides a highly informative written description of the claimed methods and the means to practice such methods in any mammalian subject. The written description of Applicants' methods is full, clear, concise and exact (which is required), but it avoids repetition of everything that is known in the art and avoids presenting a catalogue of every possible embodiment that is possible in view of the written description (which is not required). Accordingly, Applicants earnestly request reconsideration and withdrawal of the rejections under 35 U.S.C. §112, first paragraph.

Response to Rejections Under 35 U.S.C. § 102(a)

In the Office Action, Claims 40-44, 45, 47, 51, and 52 were rejected under 35 U.S.C. §102(a) as anticipated by PCT publication WO 96/39168 (Kwoh et al.).

With respect to WO 96/39168, The Examiner stated:

> "The 96/39168 publication teaches a method of modulating the endogenous active cholesteryl ester transfer protein (CETP) in a mammal such as a rabbit comprising administering to said mammal a full-length human CETP of SEQ ID NO:1 of WO 96/39168, or a [toxoid] conjugated human CETP peptide, which are non-endogenous CETP, in an amount effective to stimulate an immune response such as anti-CETP antibody wherein said antibody inhibits the function of CETP such as anti-CETP antibody wherein said antibody inhibits the function of CETP such as reducing the CETP activity below 20% of that of the untreated mammal (See abstract, Fig 2, of WO 96/39168, in particular). The reference method comprises administer[ing] to the mammal with an adjuvant . . . The reference method decreases LDL-cholesterol

> to less than 16% of the total cholesterol in the serum (blood plasma), which is about 10% (See Table 1, page 11, in particular). The term "about" expands the claimed 10% of the total cholesterol to read on the reference 16%. . . .
>
> "While the reference is silent that the reference method of administering to the mammal a whole non-endogenous CETP has the property of that recited in claims 41-43 and 45, the antibody directed against said non-endogenous CETP in the mammal and the functional properties of the reference antibody are the inherent property of the reference method. Therefore the claimed method appears to be the same as the prior art method. Since the Patent Office does not have the facilities for examining and comparing the method of the instant invention to those of the prior art, the burden is on applicant to show the prior art method is different from the claimed method. . . Thus, the reference teachings anticipate the claimed invention"

(Office Action, paragraph bridging pp. 9-10). For the reasons explained below, Applicants respectfully traverse the rejection.

For anticipation under 35 U.S.C. §102 by a printed publication, that publication must teach each and every element or aspect of the claimed invention. As explained in MPEP §2131:

> **"TO ANTICIPATE A CLAIM, THE REFERENCE MUST TEACH EVERY ELEMENT OF THE CLAIM**
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> " 'A claim is anticipated only if each and every element as set forth in the claim is found, either expressly or inherently described, in a single prior art reference.' *Verdegaal Bros. v. Union Oil Co. of California*, 814 F.2d 628, 631, 2 USPQ2d 1051, 1053 (Fed. Cir. 1987). 'The identical invention must be shown in as complete detail as is contained in the . . . claim.' *Richardson v. Suzuki Motor Co.*, 868 F.2d 1226, 1236, 9 USPQ2d 1913, 1920 (Fed. Cir. 1989)." (emphasis in original).

Applicants' claimed methods comprise administering a whole, non-endogenous CETP to a mammal to achieve an anti-atherogenic condition characterized by a heretofore unknown levels of CETP molecules, CETP activity, HDL-cholesterol, or LDL-cholesterol in the blood of the mammal.

First, Applicants note that the Example, Figure 2, and Table 1 of PCT WO 96/39168 (hereinafter, "Kwoh") describe a study in which rabbits were injected with a free, linear peptide containing the carboxy terminal 11 amino acids of a human CETP or a mixture of toxoid-

conjugated forms of the peptide in which the 11-amino acid peptide was conjugated to a diphtheria toxoid or to tetanus toxoid (see, Example 2, p. 8, line 5-p. 10, line 30 of Kwoh). Thus, unlike Applicants' invention as claimed, none of the rabbits in Kwoh was administered a whole, non-endogenous CETP protein.

Figure 2 of Kwoh shows the CETP activity in rabbits that received a free or toxoid-conjugated peptide relative to that in control rabbits that received saline. Rabbits that received free peptide showed a slight relative decrease of no more than 15% (i.e., exhibited at least 85% of the control level of CETP activity) and rabbits that received the conjugated peptides showed a relative decrease of not more than 40% (i.e., exhibited at least 60% of the control level of CETP activity). Thus, Figure 2 provides no data for a mammal that has been administered a whole, non-endogenous CETP, and, furthermore, the peptide vaccines of Kwoh are not reported to provide a blood plasma condition in which the level of CETP activity in a mammal falls below 20% of the level found in the untreated mammal. Figure 2 thus does not describe each and every element of Applicants' claimed methods, particularly with respect to Claim 40.

As with Figure 2, Table 1 on page 11 of Kwoh only provides data from Example 2 of Kwoh in which rabbits were administered a free peptide or a toxoid-conjugated peptide vaccine. The Examiner states that the data in Table 1 shows a lipoprotein profile in which about 16% of the total cholesterol is LDL-lipoprotein, apparently referring to the data for rabbits that received a free 11-amino acid peptide vaccine. Not only does Table 1 not provide any description or data of Applicants' claimed method, Table 1 does not even have one example of achieving the low level of LDL-cholesterol achieved by Applicants' method.

The Examiner provides no explanation for the interpretation of the claim term "less than about 10%" as being met by the best case 16% LDL/Total cholesterol level calculated from Kwoh Table 1 data. Applicants submit that the term "less than about 10%" sets a threshold including only values under 10% up to and not significantly exceeding 10%. The 60% excess required to reach 16% from 10% is submitted to be significant and thus not encompassed within "less than about 10%" in the context of the measurements involved. Moreover, Applicants point out that their invention call for achieving a maximum value of 10% for LDL-cholsterol, showing data where LDL-cholesterol is essentially completely eliminated, whereas the 16% level noted by the examiner is the minimum LDL-cholesterol value achieved according to Kwoh, with all other values reported in Table 1 being higher than 16%. Accordingly, Kwoh as a reference does

not meet or suggest the teaching, "less than about 10%", aside from the fact that the methods compared are different.

Furthermore, the Examiner's focus on the possible properties of the antibodies elicited in the method of Kwoh and those elicited in Applicants' claimed methods is misdirected. Persons of ordinary skill in this art who read Applicants' specification know the difference between administering a whole, non-endogenous CETP and administering the CETP peptide fragments and conjugates as described in Kwoh. The description of the peptides in Examples 1 and 2 of Kwoh clearly distinguishes the Kwoh teachings from the recitations of Applicants' claims. From consideration of Kwoh, the person of ordinary skill in the art is not informed that reduction of HDL-cholesterol to a level of less than about 10% is possible to achieve; only by using a whole non-endogenous CETP immunogen according to Applicants' disclosure can such a low level of LDL-cholesterol be achieved. This may be due to a difference in the polyclonal response to a different immunogen (CETP peptide as opposed to whole, non-endogenous CETP) or some other scientific phenomenon unknown even to Applicants: It does not matter. Kwoh does not provide a method or means for meeting Applicants' invention. The essential steps for carrying out Applicants' claimed methods are not identical to the methods described in Kwoh; Applicants' invention simply does not involve administering a peptide of Kwoh to a mammal, and the Kwoh reference does not come close to disclosing the specific endpoints expressly stated in Applicants' claims.

In conclusion, Kwoh's teaching is irrelevant to the steps that a person of ordinary skill in this art must actually perform to practice the method of Applicants' claims. Absent a teaching of each and every element of Applicants' claimed methods, Kwoh does not qualify as a reference to reject Applicants' claims as anticipated under 35 U.S.C. §102(a). Accordingly, Applicants respectfully request that the Examiner reconsider and withdraw the rejection of Applicants' claims.

In view of all of the above comments, Applicants submit that the claims of the application are in condition for allowance. Accordingly, Applicants respectfully request that the Examiner enter the amendment to the specification and pass this application to issue.

Respectfully submitted,

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Stephanie L. Leicht
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